PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing *(day/month/year)*	**07 FEBRUARY 2005 (07.02.2005)**
Applicant's or agent's file reference JL-23357-PCT	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/KR2004/002771	**30 OCTOBER 2004 (30.10.2004)**	30 OCTOBER 2003 (30.10.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC7 C07D 501/22

Applicant

CJ CORPORATION et al

1. This opinion contains indications relating to the following items:

- [X] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [X] Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.
For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material
   - ☐ a sequence listing
   - ☐ table(s) related to the sequence listing

   b. format of material
   - ☐ in wirtten format
   - ☐ in computer readable form

   c. time of filing/furnishing
   - ☐ contained in the international application as filed.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additioanl copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-6	YES
	Claims		NO
Inventive step (IS)	Claims	1-6	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-6	YES
	Claims		NO

2. Citations and explanations :

The following documents are referred to :

D1 : WO 02/68428 A1

D2 : WO 02/83692 A1

D3 : WO 03/11871 A2

D4 : The Journal of Antibiotics, 1987, 40(7), pp.991-1005

D5 : US 4699979

D1 discloses a preparation method of cephalosporin which comprises reacting a cephem compound with a 4-hydroxyphenylglycine whose carboxylic acid group is activated by pivaloyl chloride.

D2 discloses that 3-(Z)-propenyl cephem compound is selectively prepared by reacting phosphoranylidene cephem compound with actaldehyde in the presence of a base in a solvent mixture essentially comprising diethyl ether.

D3 discloses a process for the production of cefprozil (which is the same compound as the compound of formula 1 of the present invention) comprising reacting cephem compound of formula III in the form of an amidine salt with a mixed carboxylic acid anhydride of 4-hydroxyphenylglycine.

D4 describes the synthesis of BMY-28100 compound which is an 3-alkenyl derivative of 7-phenylglycyl cephalosporins. The synthetic scheme in D4 discloses that 7-amino-3-chloromethyl-3-cephem-4-carboxylate is acylated with N-BOC-protected phenylglycine in the presence of dicyclohexylcarbodiimide and Wittig reaction is performed with aldehyde in dichloromethane or chloroform in the presence of a base.

D5 discloses that the addition of lithium halide improves the proportion of Z/E isomer in Wittig reaction and acylation of 7-amino-3-propen-1-yl cephalosporin with N-BOC protected 4-hydroxyphenylglycine is carried out in the presence of dicylclohexylcarbodiimide as a coupling reagent.

(Continued on Supplemental Sheet.)

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of :

Box V.

The present invention relates to a method of preparing cephalosporin compound of formula 1 comprising the steps of (a) reacting a phosphoranylidene cephem compound of formula (4) with acetaldehyde in the presence of a base in a solvent mixture comprising water, isopropanol and methylene chloride in the ratio of 1:3~6:11~14 to give compound of formula (3) and (b) acylation of the compound of formula (3) with 4-hydroxyphenylglycine derivative of formula (4).

1. Novelty and Inventive Step

None of the prior art suggests the solvent system claimed in the present invention for raising the Z- to E-isomer ratio in Wittig reaction.
Although D2 suggests a two-phase solvent system and the organic phase thereof essentially comprising a diethyl ether for raising the Z-isomer, D2 also describes that it is difficult to raise Z-isomer content to above 83% when using a conventional organic solvent such as methylene chloride. Therefore, it is not obvious to a skilled person seeking reaction condition for raising the Z-isomer content to apply the solvent system claimed in the present invention.
Although D1 also discloses a compound of formula (2) in the present invention as an activated derivative of 4-hydroxyphenylglycine for acylation, D1 is silent about the reaction condition for improving the Z-isomer content in Wittig reaction.
Therefore, the novelty and inventive step of the present invention can be acknowledged.

2. Industrial applicability

The present invention has industrial applicability.